METHOD OF TRANSPORTING A CHIMERIC HYBRID MOLECULE ACROSS THE BLOOD BRAIN BARRIER

Cross-Reference to Related Applications

This is a division of application Serial No. 10/134,187, filed 04/26/02, as to which Applicant elected a restriction of the invention as required by an Office Action mailed on 09/23/03.

Statement Regarding Federally Sponsored Research or Development

Not applicable.

Reference to Sequence Listing, a Table, or a Computer Program Listing Compact Disk Appendix

A written Sequence Listing and a computer readable form of the sequence listing, consisting of one file named ChimericHybridAnalgesics.ST25.txt on one disk, are attached as Appendices.

Background of the Invention

Field of the Invention. The present invention lies firmly within the fields of drug, bio-effective and body treating compositions, more specifically a method for transporting chimeric hybrid molecules across the blood brain barrier. The present invention will be especially useful for transporting analgesic molecules to achieve acute and chronic pain relief.

Description of the Prior Art. The present invention relates to transporting novel hybrid alkaloid/peptide chimeric molecules across the blood brain barrier (BBB) through the use of an alkaloid moiety.

Transporting analgesic compounds across the BBB is useful for achieving efficacious analgesia. The relief of suffering due to pain is an important objective of clinical practice and for restoring quality to life and the ability to function normally to pain sufferers.

Pain represents an integrated, complex, perception of noxious stimuli originating from somatic elements such as arms and legs and/or from visceral organs such as heart and liver. Mechanistically, acute pain signaling involves noxious stimulation

of free nerve endings innervating somatic elements and/or visceral organs leading to the activation of different types of slowly-conducting afferent fibers of the A delta and C classes, terminating in the dorsal sensory spinal cord. A significantly more complex etiology underlies the initiation and persistence of chronic pain syndromes. This involves initial damage to peripheral nerves innervating somatic and visceral fields, persistent immunological challenge by cytokines and inflammatory mediators, reorganization of spinal cord and brainstem relay systems, and higher cortical adaptation.

From an established pharmacological perspective opioids remain the key agents of choice for treatment of a wide variety of acute and chronic pain states. The prototype opioid analgesic or painkiller is morphine. Morphine and morphine-related opioids produce their painkilling effects by profound pharmacological inhibition of neurons of the peripheral/sensory nervous system (PNS) and the central nervous system (CNS). The biochemical and cellular effects of morphine, including potent analgesia, are transduced through a membrane-associated G-protein designated the mu (μ) opioid receptor (MOR), found in high concentrations within the PNS and CNS. In a prior invention (U.S. Patent 5,891,842), I established a therapeutic procedure or treatment regimen for inducing or eliciting a markedly enhanced opioid-dependent

analgesic response within a living subject. That treatment methodology employs the concurrent administration of two recognized, self-contradicting and physiologically antagonistic compounds, the opioid analgesic morphine sulfate and the tachykinin peptide substance P (SP), at individual concentrations that had been empirically shown to have either marginal or completely ineffectual pharmacological properties *in vivo*. Because noxiously challenged or damaged sensory nerves release a variety of excitatory chemical mediators, including SP, the tachykinin SP had been previously designated as a nociceptive or pain-producing peptide transmitter at the spinal level. Nevertheless, my research demonstrates that at prescribed low nanogram concentrations SP appears to be a potent regulator of opioid analgesia *in vivo*.

Despite this apparent contradiction and the previously demonstrated physiological antagonism between these compounds in their traditional formats and conventionally used concentrations, my novel treatment process demonstrated a synergistic relationship over a period of time, and that an effective and efficacious opioid-induced analgesia results within the living subject from the process.

Unfortunately, because my prior invention requires the concurrent administration of two different self-contradicting and physiologically antagonistic compounds, SP and morphine, it presents difficulties in successfully establishing and testing the appropriate concurrent dosages for efficacious and safe administration in humans, as reflected by FDA and NIH clinical testing guidelines. This includes differences in the ability of morphine and of SP to cross the BBB.

While morphine is the prototype opioid analgesic or painkiller, its complex alkaloid characteristics differ greatly from those of peptides, and SP is a peptide. In subsequent research, therefore, collaborators and I combined the active pharmacological domains of SP and the peptide endomorphin-2 into one chemical entity: a novel seven amino acid peptide chimera, designated ESP7. Repeated administration of the chimeric molecule into the rat spinal cord milieu produced analgesia mediated by the MOR without a loss of potency over a 5-day time course. Essentially, ESP7 represented a non-tolerance forming compound with future potential as a specialized spinal analgesic for control of acute and/or chronic pain. (Foran, et al., A Substance P-opioid chimeric peptide as a unique non-tolerance-forming analgesic, 97 Proceedings of the National Academy of Sciences 13 (2000))

Although ESP7 provided the advantage of a single analgesic molecule, it has several unfortunate disadvantages. Operationally, the peptide chemical nature of ESP7 restricts its effective dosage and time-effect relationship within the CNS due to significant metabolism in the blood stream. This is supported by collected pharmacological data indicating significant difficulties encountered by peptide drug candidates for crossing the mammalian BBB (Egleton RD, Abbruscato TJ, Thomas SA, Davis TP Transport of opioid peptides into the central nervous system. J Pharm Sci 1998; 87(11):1433-9).

Morphine is a relatively complex organic molecule, termed an alkaloid due to its positively charged nitrogen group, unlike the endogenous peptide endomorphin-2 which provided the analgesic moiety in ESP7. Morphine is a highly efficacious MOR-selective opioid analgesic and will cross the human BBB, as will its active metabolite morphine 6-glucuronide. (Stain-Texier F, Boschi G, Sandouk P, Scherrmann JM, Elevated concentration of morphine 6-beta-D-glucuronide in brain extracellular fluid despite low blood-brain barrier permeability. Br J Pharmacol 1999; 128(4):917-24)

Substance P, however, is a peptide. Chimeric hybrid molecules possessing an alkaloid moiety and a peptide moiety are unknown to the literature of analgesia and to clinical practice. Chimeric

hybrid molecules possessing an alkaloid moiety to activate the human MOR and a peptide moiety to concurrently activate the human SP receptor (SPR) are unknown to the literature of analgesia and to clinical practice. Chimeric hybrid molecules comprised of one moiety with a chemically modified morphine molecule to activate the human MOR and another moiety with a SP fragment to activate the human SPR are unknown to the literature of analgesia and to clinical practice. The method of inhibiting the development of opioid tolerance using such chimeric hybrid molecules is unknown to the literature of analgesia and to clinical practice.

Another major challenge is to design a molecule that will cross the BBB and produce analgesia in a living subject, while inhibiting tolerance development and dependence formation. Peptides do not readily cross the BBB. To achieve the analgesic effects I envisioned, a chimeric compound that activates both an MOR and SPR must cross the BBB. Such a molecule should be structured in such a way as to activate simultaneously the MOR and SPR domains in the PNS and/or CNS. With respect to both morphine and SP, a variety of alkaloid morphine and SP peptide fragments can be synthesized, having potentially different pharmacological effects if bound to another moiety. No obvious method is known for the SP moiety to be cross-linked to a morphine alkaloid moiety in a fashion that the resulting molecule will allow simultaneous

activation of both the MOR and SPR receptors. Chimeric hybrid molecules with a moiety comprised of a chemically modified morphine molecule to provide the method to transport active SP fragments across the mammalian blood brain barrier are unknown to the literature of analgesia and to clinical practice.

Presently there also are no analgesic opioid chimeras that have crossed the BBB to achieve effective analgesia for mammalian acute or chronic pain without significant tolerance development and dependence formation.

Objects and Advantages. I have invented novel and useful methods employing heretofore unknown morphine-SP hybrid chimeras, as I have described below. Several objects and advantages of my present invention are:

a. a method for transporting, across the BBB, a molecule that can be dosed to produce effective analgesia in a living subject, *i.e.*, a mammal (an animal class which includes humans), while inhibiting tolerance development;

b. a method for transporting, across the BBB, a molecule that can be dosed to produce effective analgesia in a living subject while inhibiting dependence formation;

c. a method for transporting, across the BBB, a molecule that can be dosed to produce effective opioid analgesia and that can be administered through a variety of methods of clinical administration, including oral, systemic and intrathecal administration;

d. a method for transporting, across the BBB, a molecule that can be dosed to produce effective opioid analgesia without significant restriction on its effective dosage and time-effect relationship within the CNS due to metabolism in the blood stream;

e. a method for transporting, across the BBB, a molecule that can be dosed to yield effective opioid analgesia with a reduction in the likelihood of undesirable side effects;

f. a method for transporting, across the BBB, a molecule that can be dosed to produce effective opioid analgesia with a reduction in the likely severity of undesirable side effects that become manifested by the patient;

g. a method for transporting, across the BBB, an opioid analgesic that can be dosed for administration to children without undue tolerance development;

h. a method for transporting, across the BBB, an opioid analgesic that can be dosed for administration to children without undue dependence formation; and

i. a method for transporting, across the BBB, an opioid analgesic suitable for PCA in the treatment of chronic and/or acute pain.

Additional objects and advantages of my present invention are:

a. to provide a method for transporting a chimeric molecule across the BBB so as to treat pain with opioid analgesia and little or no opioid tolerance development;

b. to provide a method for transporting a chimeric molecule across the BBB so as to treat pain with opioid analgesia and little or no opioid dependence formation;

c. to provide a method for transporting a chimeric molecule across the BBB so as to treat pain with opioid analgesia with reduced likelihood of undesirable side effects;

d. to provide a method of transporting a chimeric molecule across the BBB so as to provide opioid analgesia for PCA for acute and/or chronic pain; and

e. to provide a method of transporting a chimeric molecule across the BBB so as to treat drug abuse by administering as a substitute for the abused drug an analgesic that elicits little or no tolerance development or dependency formation and thereafter adjusting the dosage as tolerance and/or dependence is modulated.

Still further objects and advantages will become apparent from a consideration of the following description of my invention.

Brief Summary of the Invention

The present invention provides a method of transporting novel chimeric hybrid molecules across the BBB by using an opioid moiety of chemically modified morphine. A useful feature of this method is that it can be used to transport across the BBB a chimeric hybrid molecule in which an opioid moiety binds to and activates an MOR and a SP peptide fragment moiety binds to and activates an SPR.

The present invention provides a method for transporting a chimeric hybrid molecule across the BBB. The method utilizes a family of chimeric hybrid molecules in which the alkaloid morphine or its active metabolite morphine 6-glucuronide are by design

carriers of another moiety (such as active SP peptide fragments) across the mammalian BBB. I have designed this heretofore-unknown method of transporting a chimeric hybrid molecule across the BBB by suing a family of hybrid, chimeric molecules with unique molecular hinges. This novel family of chimeric hybrid compounds can provide opioid analgesia in living subjects while inhibiting tolerance development and dependence formation. These chimeric hybrid compounds can also be used for drug abuse treatment. The hybrid alkaloid/peptide analgesics may be administered systemically, intrathecally or more preferably, orally.

In one embodiment, the independent functional domains consisting of chemically modified morphine and a SP fragment are covalently cross linked through the four carbon organic molecule succinic acid. In another embodiment, the independent functional domains consisting of chemically modified morphine and a SP fragment are covalently cross linked through the four carbon organic molecule gamma-hydroxy butyric acid. In another embodiment, the independent functional domains consisting of chemically modified morphine and a SP fragment are covalently cross linked through the six carbon carbohydrate d-glucuronic acid. The use of three such molecules, succinic acid, gamma-hydroxy butyric acid, and d-glucuronic acid, as molecular hinges to cross link two active pharmacological domains of disparate chemical nature, i.e., a

multi-ringed opioid alkaloid structure and a linear peptide structure, is not intuitively obvious or predictable from the prior art. The use of succinic acid, gamma-hydroxy butyric acid, and d-glucuronic acid, as molecular hinges to cross link a pharmacologically active peptide to a pharmacologically active opioid is novel and unknown to the literature of analgesia and to clinical practice. The use of this method of linking an opioid alkaloid structure in a chimeric hybrid molecule so as to transport the molecule across the BBB is unknown to the literature of analgesia and to clinical practice.

The chimeric hybrid molecule may be designed to have a plurality of SP moieties consisting of pharmacologically active COOH-terminal fragments of SP and a plurality of opioid alkaloid moieties consisting of morphine chemically modified at its 6'hydroxyl group. The plurality of opioid moieties are each designed to bind to and activate an MOR. The plurality of SP fragments are each designed to bind to and activate an SPR. Because the MOR- and SPR-activating domains are of chemically different compositions, i.e., a multi-ringed alkaloid structure and a linear peptide structure, respectively, it is not intuitively obvious that they may be combined in a functionally active molecule. This is achieved, however, by incorporating a novel molecular hinge region consisting of succinic acid, or

gamma-hydroxy butyric acid, or d-glucuronic acid. The existence of functionally active chimeric hybrid molecules, of internally differing chemical nature, combining MOR- and SPR- activating domains linked by a novel molecular hinge are unknown to the literature of analgesia and to clinical practice.

The invention provides a method for transporting the chimeric hybrid molecules across the BBB using pharmaceutical compositions including hybrid alkaloid chimeric molecules and a pharmaceutically acceptable carrier useful for the treatment of pain. It represents methods of treating pain using novel hybrid alkaloid/peptide chimeric molecules containing an opioid and SP moiety designed to achieve coincident activation of populations of MORs and SPRs as a novel pain treatment without tolerance and dependence. The hybrid alkaloid/peptide analgesics may be administered systemically or more preferably, orally. Solubility, absorption, and penetration through the human BBB will be markedly enhanced due to the hydrophilic properties of morphine. The invention therefore provides novel methods for treating pain using chemically modified morphine to serve both as an opioid analgesic as well as a pharmaceutically acceptable carrier for SP peptide absorption and stability after systemic administration as well as penetration through the human BBB. In these novel attributes, the method of inhibiting opioid tolerance development using hybrid

alkaloid chimeric molecules differs substantially from prior art including the use of peptide ESP7.

The method of transporting novel chimeric hybrid molecules across the BBB by using chimeric hybrid molecules that encompass three chemically disparate functional domains, i.e., a ringed alkaloid MOR-activation domain, a peptide SPR-activation domain, and a flexible organic acid hinge domain, is unknown to the preclinical and clinical literature of pain and analgesia.

A desired objective of the present invention is that it will transport a chimeric hybrid molecule across the BBB such that the hybrid alkaloid/peptide chimeric molecules can be administered to produce clinically efficacious opioid analgesia with little or no development of opioid tolerance. With little or no tolerance development, escalating dosages will not be required to achieve the same pain killing effect and opioid dependence formation and undesirable side effects associated with escalating opioid dosages will be avoided or markedly reduced.

Detailed descriptions of one or more embodiments of the invention are described below. The novelty of the invention, as amply described above, will be apparent from the detailed description of structure and synthesis and from the claims. In the specification

and the appended claims, the singular forms include plural referents unless the context clearly dictates otherwise. All technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Unless expressly stated otherwise, the techniques employed or contemplated herein are standard methodologies well known to one of ordinary skill in the art. The examples of embodiments are for illustration purposes only. All patents and publications cited in this specification are incorporated herein by reference.

Brief Description of the Drawings

Fig. 1 illustrates two domains of the morphine nucleus, one being a conjugation domain useable to synthesize the chimeric hybrid compounds and the other being the active domain that activates the MOR.

Fig. 2 illustrates schematically how a chimeric hybrid molecule is constructed of three, linked components, i.e., a morphine nucleus, a linker-hinge and an SP fragment.

Detailed Description of the Invention

Description - Figs 1 and 2. The present invention provides a method of transporting a chimeric hybrid molecule across the BBB so as to inhibit the development of opioid tolerance using hybrid alkaloid chimeric molecules having an MOR binding and activation moiety and an SPR binding and activation moiety. The hybrid alkaloid chimeric molecules are designed to cross the BBB. They can thus bind to and activate populations of MORs and SPRs located primarily within the human CNS, but also in the human PNS, involved in pain mediation and analgesic responses. While the alkaloid morphine and the peptide SP frequently exhibit slight cross reactivity to other opioid and tachykinin receptor types, respectively, they are generally characterized, as exhaustively detailed in the literature, by a very high degree of affinity for the MOR and SPR, respectively. The preservation of independent binding and activation moieties in one hybrid alkaloid/peptide molecule containing a multi-ringed alkaloid structure and a linear peptide structure, is not described in the prior art and distinguishes the present invention as novel and not evolving from prior invention.

The existence of functionally active chimeric hybrid molecules, of internally differing chemical nature, combining MOR- and SPR-activating domains linked by a novel molecular hinge are unknown to the literature of analgesia and to clinical practice. Because

the MOR- and SPR-activating domains are of chemically different compositions, i.e., a multi-ringed alkaloid structure and a linear peptide structure, respectively, it is not intuitively obvious that they may be combined in a functionally active molecule using the alkaloid moiety to transport the molecule across the BBB.

I have achieved this by design and incorporation of a novel chemical linker-hinge region consisting of succinic acid, or gamma-hydroxy butyric acid, or d-glucuronic acid, to connect within a single molecule an alkaloid MOR-activation domain and a peptide SPR- activation domain that are modified to be compatible with that hinge. The design of novel hybrid alkaloid chimeric molecules encompassing three chemically disparate functional domains, i.e., a ringed alkaloid MOR-activation domain, a peptide SPR-activation domain, and a flexible organic acid hinge domain, is unknown to the preclinical and clinical literature of pain and analgesia. The use of such hybrid alkaloid chimeric molecules to inhibit the development of opioid tolerance is unknown to the preclinical literature and clinical literature of pain and analgesia.

The chimeric multi-ringed alkaloid structure of morphine linked to the linear peptide structure of SP is illustrated in Fig. 1 and Fig. 2. Fig. 1 illustrates that a morphine nucleus can be

considered as divided into two domains, one of which is a conjugation domain **2** useable to synthesize the chimeric hybrid compounds from the 6'OH position on the morphine nucleus and the other of which is an active domain **1** that activates the MOR. Fig. 2 illustrates schematically how a chimeric hybrid molecule is constructed of three interlocking components, the alkaloid morphine nucleus **3**, a chemical- linker hinge **4**, and a peptide SP fragment **5**. The chemical linker-hinge **4** links to the alkaloid morphine nucleus **3** at its 6'OH position. The chemical linker-hinge **4** also links to the peptide SP fragment **5**. The linker-hinge allows the N-terminal opioid receptor binding moiety or active domain of the morphine nucleus fragment of the hybrid chimeric molecule be able to activate an MOR and the C-terminal SP receptor agonist binding moiety of the SP fragment to be able to activate an SPR.

The method employs chimeric hybrid molecules that may be designed to have a plurality of SP moieties consisting of pharmacologically active COOH-terminal fragments of SP and a plurality of opioid alkaloid moieties consisting of morphine chemically modified at its 6'hydroxyl group. The plurality of opioid moieties are each designed to bind to and activate an MOR. The plurality of SP fragments are each designed to bind to and activate an SPR.

I refer to the following amino acid sequences using the Seq. Id. Nos. below:

SEQ. ID. NO.	SEQUENCE
1	Lys Pro Gln Gln Phe Phe Gly Leu Met
2	Gln Gln Phe Phe Gly Leu Met
3	Phe Phe Gly Leu Met

Nine preferred embodiments of chimeric hybrid analgesics which the method of the present invention can employ are listed in table 1

Table 1:

Embodiment #	μ receptor agonist	Hinge	SP receptor agonist	Sequence
1	Morphine	D-Glucuronic Acid	N-AcetylsubstanceP[3-11]: Ac-KPQQFFGGLM-NH2	SEQ. ID. NO. 1
2	Morphine	D-Glucuronic Acid	Substance P [5-11]: QQFFGLM-NH2	SEQ. ID. NO. 2
3	Morphine	D-Glucuronic Acid	Substance P[7-11]: FFGLM-NH2	SEQ. ID. NO. 3
4	Morphine	Succinic acid	N-AcetylsubstanceP[3-11]: Ac-KPQQFFGLM-NH2	SEQ. ID. NO. 1
5	Morphine	Succinic acid	Substance P [5-11]: QQFFGLM-NH2	SEQ. ID. NO. 2
6	Morphine	Succinic acid	Substance P[7-11]: FFGLM-NH2	SEQ. ID. NO. 3
7	Morphine	Gamma-OH Butyric Acid	N-AcetylsubstanceP[3-11]: Ac-KPQQFFGLM-NH2	SEQ. ID. NO. 1

8	Morphine	Gamma-OH Butyric Acid	Substance P [5-11]: QQFFGLM-NH2	SEQ. ID. NO. 2
9	Morphine	Gamma-OH Butyric Acid	Substance P[7-11]: FFGLM-NH2	SEQ. ID. NO. 3

Advantages of The Present Invention.

The advantages of morphine as an analgesic that can cross the BBB are well known to the literature. The advantages of simultaneous activation of an MOR and SPR to modulate the activation of the MOR and to reduce or eliminate tolerance development and dependence formation are also known from the literature, such as a prior invention of mine (U.S. Patent 5,891,842) and the work of colleagues of mine and I identified above relating to ESP7.

From the description above, a number of advantages of my method of inhibiting opioid tolerance development using chimeric hybrid analgesic molecules becomes evident:

a. the method will transport a chimeric hybrid molecule across the BBB so as to inhibit tolerance development while being dosed to provide morphine opioid analgesia;

b. the method will transport a chimeric hybrid molecule across the BBB so as to inhibit dependence formation

while being dosed to provide morphine opioid analgesia;

c. the method can be used by means of administration of the molecules through a variety of methods of clinical administration, in addition to intrathecal administration;

d. the method will not have the significant dosage and time-effect restrictions of peptides due to metabolism in the blood stream;

e. because of the modulation of an MOR by SPR activation, an escalating dosage typical of morphine is not required;

f. because the escalating dosage typical of morphine is not required, the likelihood and severity of undesirable effects associated with escalating morphine dosage will be reduced; and

f. the method can be used to administer a chimeric hybrid analgesic molecule as a substitute for an abused opioid drug and, because the molecule elicits little or no tolerance development or dependency formation, its dosage can thereafter be adjusted as tolerance and/or dependence is modulated.

Further advantages will become apparent to those skilled in the art.

Making My Invention. The present invention can be made by a person skilled in the art, as follows. The method uses chimeric hybrid analgesic molecules to inhibit the development of opioid tolerance. The separate MOR- and SPR-activating moieties are synthesized and purified or isolated from natural sources and then chemically cross-linked to form hybrid alkaloid/peptides chimeric molecules. All syntheses utilize well-established standard organic chemistry techniques and reagents. SP peptide fragment moieties are synthesized prior to covalent attachment to the morphine nucleus (Fig. 1). For these purposes, a variety of peptide synthesis methods are common in the art, including synthesis using an automated peptide synthesizer and employing Fmoc amino acids. (Merrifield, Science 232: 241-247 (1986); Barany, et al, Intl. J Peptide Protein Res. 30: 705-739 (1987); Kent, Ann. Rev. Biochem. 57:957-989 (1988), and Kaiser, et al, Science 243: 187-198 (1989)) SP peptide fragments are purified to over 99% chemical purity using standard peptide purification techniques such as reverse-phase high-pressure liquid chromatography (HPLC). The chemical structures of SP peptide fragments, purified by HPLC, are confirmed by mass spectroscopic analysis.

Morphine is chemically modified by covalent attachment at its 6'OH group to the hinge-forming organic molecules described above: d-glucuronic acid, succinic acid, gamma-hydroxy butyric acid.

Chemically modified morphine derivatives, i.e., morphine-6-glucuronide, morphine-6-hemi-succinate, morphine-6-gamma-hydroxy butyrate, are covalently attached to SP peptide fragments using standard condensing agents such as water soluble carbodiimide (CDI).

Alternatively, SP peptide fragments are chemically modified by covalent attachment at their free amino groups to the hinge-forming organic molecules described above: d-glucuronic acid, succinic acid, gamma-hydroxy butyric acid. Chemically modified SP peptide fragments, i.e., SP fragment-glucuronide, SP fragment-hemi-succinate, SP fragment-gamma-hydroxy butyrate, are covalently attached to morphine using standard condensing agents such as water soluble CDI.

Prior to pharmacological testing, the novel chimeric hybrid alkaloid/peptide molecules comprising a cyclic alkaloid MOR-activating moiety and an SPR-activating peptide moiety (such as those in Table 1) are purified to over 99% purity by standard chromatographic techniques such as reverse-phase HPLC. This represents less than about 1% chemical precursors or non-peptide chemicals in the final preparations. The chemical structures of chimeric hybrid alkaloid/peptide molecules are confirmed by mass

spectroscopic analysis. The chimeric hybrid molecules are then subjected to standard pharmacological testing.

Preclinically, a well-established method is used to assess the analgesic properties of the novel chimeric hybrid compounds, that being the tail flick test, which is administered to rats following parenteral or CNS administration. Additional tests of analgesic responsiveness include the paw withdrawal and hotplate tests, i.e., methods well-established as common in the art. Preclinical testing of analgesia and tolerance development is conducted by administration of the chimeric hybrid compounds over time and alternatively using opioid and SP blockers in well-established analgesic testing methods. Further preclinical and clinical testing is conducted in conformity with governmental drug regulations.

Having made the chimeric hybrid molecules, they are administered to inhibit the development of opioid tolerance through means of clinical administration of analgesia well known to persons skilled in the art.

Using My Invention. The present invention further provides a method of transporting a across the BBB chimeric hybrid molecules for treating a mammal for relief of pain by administering a

pharmaceutical composition (as described above) in order to produce analgesia in the subject/patient. The invention is used by persons skilled in the art, as follows: Pharmaceutical compositions of the invention are formulated to be compatible with their intended routes of administration, e.g., parenteral, intrademal, subcutaneous, injectable, intravenous, oral, intradermal, subcutaneous, transdermal (topical), transmucosal, and rectal administration.

Solutions or suspensions suitable for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or

dispersion. For intravenous administration, suitable carriers include physiological saline, sterile or bacteriostatic water, or phosphate buffered saline (PBS). In all cases, the compositions must be sterile and should be fluid to the extent that they are easily injectable by syringe. Proper fluidity may be maintained by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Preservation of chemical and pharmaceutical integrity is achieved by various antibacterial and antifungal agents: e.g., parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, etc. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound (e.g., chimeric hybrid molecules) in the required dosage in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization.

Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with binders and used in the form of tablets, troches, or capsules. Pharmaceutical binding agents, and/or adjuvant material can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide.

Suitable intradermal, subcutaneous, transdermal (topical), and transmucosal formulations include: gels, creams, solutions, emulsions, suspensions, carbohydrate polymers, biodegradable matrices thereof, vapors, mists, aerosols and other inhalants, and skin patches. Rectal formulations also include suppositories and enemas.

Examples of suitable pharmaceutical carriers for the various forms of administration include any of the standard pharmaceutically accepted carriers known to those of ordinary skill in the art.

Examples of pharmaceutical carriers include but are not limited to buffered saline solution, water, emulsions, various wetting agents, tablets, coated tablets and capsules. Besides an effective amount of the compounds described in the present invention, pharmaceutical compositions may include suitable diluents, preservatives, solubilizers, emulsifiers, adjuvant and/or carriers. Examples of optional ingredients which may be included in the pharmaceutical compositions of the present invention include antioxidants; low molecular weight polypeptides; proteins such as serum albumin, gelatin or immunoglobulins; amino acids such as glycine; chelating agents; sugar alcohols.

Because of the modulation of opioid tolerance and dependence, the invention may also be used for drug abuse intervention through administration of one or more embodiments of the chimeric hybrid analgesics which are the subjects of the invention in substitution for the drug to which the patient became tolerant and/or on which the patient became dependent.

Conclusions, Ramifications and Scope. The reader thus will see that my invention provides a novel and useful method for transporting chimeric hybrid molecules across the BBB.

While my description contains many specifications, these should not be construed as limitations on the scope of my invention, but rather as an exemplification of one or more of the preferred embodiments of my invention. Other variations are possible. Accordingly, the scope of my invention should be determined by the appended claims and their legal equivalents and not by the embodiments illustrated in the foregoing description.